UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,475	10/10/2001	Ryuichi Morishita	6235-59221	4309

24197 7590 06/17/2005

KLARQUIST SPARKMAN, LLP
121 SW SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,475	MORISHITA ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11,12,14,16,23-27 and 44-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11,12,14,16,23-27,44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/17/05,2/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 9, 11, 12, 14, 16, 23-27, and 44-47 are pending.

Applicant's traversal, the cancellation of claims 22 and 28-43, the amendment to claims 9 and 23, and the addition of claims 44-47 in paper filed on 3/17/05 is acknowledged and considered.

The Declaration of Ryuichi Morishita and Toshio Ogihara under 37 CFR 1.132 filed 3/17/05 is sufficient to overcome the rejection of claims 9, 11, 12, 14, and 23-26 based upon 102(e) rejection.

Election/Restrictions

The instant application contains species in claim 11, 24, and new claim 45 drawn to nonelected species with traverse in paper filed on 7/7/02.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 2/7/05 and 3/17/05 was filed after the mailing date of the non-final rejection on 9/17/04. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16 and 27 remain and claims 9, 11, 12, 14, and 23-26 and new claims 44-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation 'wherein at least 50μg of the nucleic acid encoding HGF is administered to the subject' in instant claims 16 and 27 remains not supported by the instant specification. There appears to be no written description of a method for the treatment of diabetic ischemic disease in a subject comprising administering a nucleic acid encoding HGF once every few weeks or once every few days, wherein at least 50μg of the nucleic is administered to the subject in the application as filed. There is no page cited for support of the claims. See MPEP § 2163.06. The only part of the specification that might be associated with the claims is found on page 9, lines 28-36 and page 12, experiment 1. On page 9, the applicants contemplate range of dosage and amount of time the agent can be administered. On page 12, the applicants teach administering a nucleic acid encoding HGF (50μg) once into rats. The specification does not lead one skilled in the art to administering a nucleic acid encoding HGF (50μg) every few weeks or once every few days or into animals other than rats. Citing the working example on page 12 in the specification as file for support of the claimed methods, as now recited, is overreaching

because the instant specification does not disclose that administering 50μg is a general teaching that is generally applicable to the claimed methods. Therefore, there is nothing in the specification that supports the in vivo methods as set forth in the claims.

"It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

New claims 44-47 are not supported by the instant specification. There appears to be no written description for a method for the treatment of diabetic ischemic disease in a subject comprising administering a therapeutically effective amount of **a nucleic acid encoding HGF** to the muscle of an ischemic site, wherein at least **50μg of the nucleic acid encoding the HGF is administered to the subject**, thereby treating the diabetic ischemic disease in the application as filed. See MPEP § 2163.06. Applicants site page 2, lines 29-31, page 6, line 36, page 8, lines 29-35, page 9, lines 7-12 and lines 28-34, page 11, line 32 to page 12, line 15 and on page 14, lines 2-4.

On page 2, applicants contemplate using a HGF gene and not a nucleic acid encoding HGF. On page 6, applicants contemplate using HVJ-liposome and this contemplation does not support the claimed method. On page 8, applicants contemplate what types of diabetic ischemic disease can be treated with the method. On page 9, lines 7-12, the applicants contemplate administering into the blood vessel or into the muscle of the ischemic site and this contemplation does not support using a genus of administration routes embraced in the method in instant claims 44-47. On page 9, lines 28-34, applicants contemplate the dosage of the therapeutic agent (HGF

gene) and do not provide support for using a nucleic acid encoding HGF. On page 11, line 32-page 12, line 15, the applicants teach administering HGF gene (50μg) once into rats and do not provide support for treating a genus of subjects using at least 50μg of the nucleic acid encoding HGF. The instant specification does not lead one skilled in the art to administering a nucleic acid encoding HGF (50μg) into a genus of subjects. Citing several pages in the specification as filed for support of the claimed methods, as now recited, is overreaching because the instant specification does not disclose: that a nucleic acid encoding HGF is the same as a HGF gene because the term "nucleic acid encoding HGF" is broader than the term "HGF gene". In addition, using a genus of administration routes to the subject is not supported by the instant specification because the specification only discloses IM administration of 50μg of HVJ-liposome-HGF gene to a rat. 50μg of a nucleic acid encoding HGF is broader than what is disclosed in the specification (HVJ liposome containing 50μg of the HGF gene). Furthermore, the expression of HGF requires a promoter and the specification only discloses using a HGF gene and does not disclose if a nucleic acid encoding HGF consists of a promoter to express the HGF. Therefore, there is nothing in the specification that supports the in vivo methods as set forth in the instant claims.

Upon further consideration and for the reasons set forth above, the limitation 'a nucleic acid encoding hepatocyte growth factor' in instant claims 9, 11, 12, 14, 16, and 23-27 is not supported by the instant specification. In addition, the limitation was introduced in amendment filed on 6/28/01 and applicants did not cite support for the limitation.

It is apparent that the applicants at the time the invention was made did not intend or contemplate using the methods cited in the claims as part of the disclosure of their invention.

There is no evidence in the specification as filed that the applicants were in possession of the claimed methods as set forth in the claims 9, 11, 12, 14, 16, 23-27 and new claims 44-47, as it is now claimed, at the time the application was filed.

Applicant's arguments filed 3/17/05 have been fully considered but they are not persuasive because applicant provides no new arguments and applicant's argument citing page 9, lines 28-33 for support of the claims was already addressed in the previous rejection on the record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 11, 12, 14, 16, 23-27 and 44-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed methods read on using a nucleic acid encoding hepatocyte growth factor (HGF) to treating diabetic ischemic disease in a subject. The claims will therefore be evaluated based upon gene therapy for treating a diabetic ischemic disease in a subject.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (United States v. Telectronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather a conclusion reached by many factors. These factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in In Re Wands (see above).

The applicant teaches IM delivery of HVJ-liposome-HGF gene to diabetic lower limb rats (page 12). The result of the delivery of HVJ-liposome-HGF resulted in production of blood vessels in the ischemic site. This would indicate to the skilled artisan that the HGF gene contained an endogenous promoter to express the coding sequence. The prior art teaches that the skilled artisan can use a nucleic acid encoding HGF to grow blood vessels in a subject, wherein the nucleic acid is operatively linked to a promoter. See Isner et al. (WO 98/19712, cited on a PTO-1449). The claimed methods recite a nucleic acid encoding HGF, but the claims do not recite whether the nucleic acid is operatively linked to a promoter. Furthermore, with respect to the instant claims, the claims encompass using a nucleic acid encoding HGF in the method for the treatment of diabetic ischemic disease, wherein the nucleic acid is not operatively linked to a promoter. The instant specification provides sufficient guidance for one skilled in the art to make and use a HGF gene in the claimed method. However, the instant specification fails to provide sufficient guidance and/or factual evidence for one skilled in the art to make and use a

nucleic acid encoding HGF, which expresses HGF, wherein the nucleic acid is not operatively linked to a promoter (endogenous or exogenous promoter). The teachings in the instant specification are directed to using HGF gene to express HGF and not a nucleic acid encoding HGF. The specification as filed provides sufficient guidance and/or factual evidence for how to make and use HGF gene to direct HGF expression, however the claims do not recite such a structural limitation. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

In conclusion, the instant specification and the claims coupled with the art of record at the time the invention was made do not provide enablement for the claimed invention. The claimed method encompassing using a nucleotide sequence encoding HGF is not considered enabled for the reasons set forth above. Given that expressing HGF using a nucleic acid encoding HGF not operatively linked to a promoter was unpredictable at the time the invention was made, and given the lack of sufficient guidance for producing expression of the HGF in a subject, wherein there is no promoter operatively linked to the nucleic acid, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the claimed invention based on the applicant's disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9, 11, 12, 23, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner et al. (WO 98/19712, cited on a PTO-1449) taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) (cited on an PTO-1449) in further of Li et al. (US 6,066,123).

Isner teaches a method of treating limb ischemia in a subject using a nucleic acid encoding an endothelial cell mitogen selected from growth factor proteins, including hepatocyte growth factor (HGF). See pages 16-17. However, Isner does not specifically teach using a nucleic acid encoding HGF to treat diabetic lower limb ischemic disease in a subject. In

addition, Isner does not specifically teach administering the nucleic acid once every few weeks or every few days to the subject.

However, at the time the invention was made, the problems with blood circulation deficiency in lower limb diabetic ischemic disease was well known to one of ordinary skill in the art. See English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98. In addition, there was a reasonable expectation of success for gene therapy using a nucleic acid encoding HGF to treat diabetic lower limb ischemic disease. See English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98.

In addition, at the time the invention was made, short-term expression of a nucleic acid *in vivo* because of the short half-life of HGF and/or nucleic acid, and/or inactivation of the nucleic acid, and/or natural maturation and sloughing off of the transformed cell was well known to one of ordinary skill in the art and several applications (e.g., every few days or every few weeks) of the nucleic acid would be required to treat the ischemic disease in the subject. See Li et al. (column 8).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98 in further view of Li et al., namely to use a nucleic acid encoding HGF in a method of treating lower limb ischemic disease in a subject. One of ordinary skill in the art would have been motivated to combine the teachings and use a nucleic acid encoding HGF in the method because of the problems with blood circulation is associated with lower limb diabetic ischemic disease and

HGF is well known to one of ordinary skill in the art for treating problems with blood circulation.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98 in further view of Li et al., namely to administer a nucleic acid encoding HGF once every few days or every few weeks for treating lower limb ischemic disease in a subject. One of ordinary skill in the art would have been motivated to combine the teachings and administer the nucleic acid encoding HGF once every few days or few weeks because of the problems associated with delivering nucleic acid in vivo. The instant application does not teach any unexpected results when administering the nucleic acid encoding HGF once every few weeks or once every few days.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 9, 11, 12, 23, 24, and 25 have been considered but are moot in view of the new ground(s) of rejection.

Claims 9, 14, 23, 24, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner et al. (WO 98/19712, cited on a PTO-1449) taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) (cited on an PTO-1449) and Li et al. (US 6,066,123) as applied to claims 9, 11, 12, 23, 24, and 25 above, and further in view of Dzau et al. (US 5,631,237).

Isner taken with the Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section and Li do not specifically teach administering the nucleic acid to a subject with lower limb diabetic ischemia using a Sendai virus (HVJ)-liposome.

However, at the time the invention was made, administering a nucleic acid using a Sendai virus (HVJ)-liposome was well known to one of ordinary skill in the art as exemplified by Dzau et al. (columns 2-6). Dzau et al. teach that HVJ-liposome are well known to one of ordinary skill in the art for delivering DNA to vasculature4 cells (abstract).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner et al. taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) and Li et al. in further view of Dzau et al., namely to use HVJ-liposome for delivering a nucleic acid encoding HGF in the method. One of ordinary skill in the art would have been motivated to combine the teachings, as a matter of designer's choice, and use HVJ-liposome for introducing the nucleic acid into the subject because HVJ-liposome is well known to one of ordinary skill in the art for improving DNA delivery of a liposome comprising DNA to a cell. In addition, HVJ-liposome was well known to one of ordinary skill in the art for delivering DNA to vascular cells as exemplified by Dzau et al. (abstract and columns 2-6).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 9, 14, 23, and 26 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Claims 16, 27, and 44-47 are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman

JOSEPH WOITACH, PH.D.
PRIMARY EXAMINER

/Joe Woitach/

AU 1635